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Direct *C*2-trifluoromethylation of indole derivatives catalyzed by copper acetate

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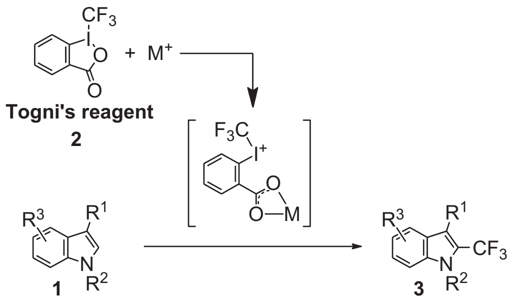
ABSTRACT

Direct *C*2-selective trifluoromethylation of indole derivatives was achieved with Togni's hypervalent iodine reagent and CuOAc as a catalyst in MeOH under mild conditions, affording the desired *C*2-trifluoromethylated indoles in good yield (up to 90%).

Introduction of fluorine into organic compounds generally results in significant changes of molecular properties, such as higher hydrophobicity and metabolic stability. In particular, trifluoromethylated compounds have become increasingly important in the pharmaceutical, agrochemical, and material science fields.[1] Therefore, intensive efforts have been made to develop direct trifluoromethylation of a wide variety of organic molecules.[2] These trifluoromethylation reactions can be classified into nucleophilic, electrophilic, and radical types. Among them, electrophilic reactions are still a developing area, and two major types of electrophilic trifluoromethylation reagents, sulfonium salt type[3] and hypervalent iodine type,[4] have been investigated.

On the other hand, the indole framework is a privileged core structure found in many natural products and bioactive compounds and its trifluoromethylated derivatives have potential pharmaceutical applications.[5] Development of synthetic methods for trifluoromethylated indole derivatives is, accordingly, a topic of current interest.[6,7] However, direct trifluoromethylation of indole derivatives is still challenging.[8–10] Indole derivatives have generally been used as nucleophiles, but it is well known that indole has several reactive sites, that is, regioselectivity is an issue in indole functionalization. The problem of regioselectivity has been overcome in some C–C bond formation reactions by using metal- or organo-catalysts.[11] In addition, Togni and MacMillan noted that hypervalent iodine reagent showed increased electrophilicity in the presence of a Lewis acid.[12,13] Inspired by these findings, we examined the regioselective trifluoromethylation of indole derivatives using hypervalent iodine and a metal catalyst (Scheme 1).[14] Herein, we report copper-catalyzed *C*2-selective trifluoromethylation of indole derivatives with hypervalent iodine reagent (Togni's reagent).

Trifluoromethylation of 3-methylindole was initially examined in the presence of Togni's reagent **2**[4] and a catalytic amount of various metal salts at room temperature under an argon atmosphere (Table 1). No reaction was observed in the absence of metal catalyst (entry 1).[15] The reactions with $Co(OAc)_2$, $Ni(OAc)_2$, and $Zn(OAc)_2$ provided *C*2-trifluoromethylation product **3a**, albeit with low yield (entries 3, 4, and 6). $Fe(OAc)_2$ and $Cu(OAc)_2$ gave better



Scheme 1. Trifluoromethylation of indole derivatives.

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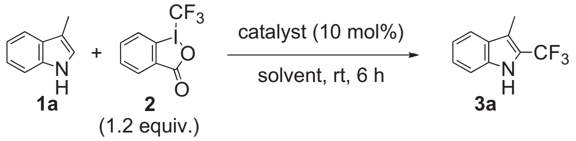
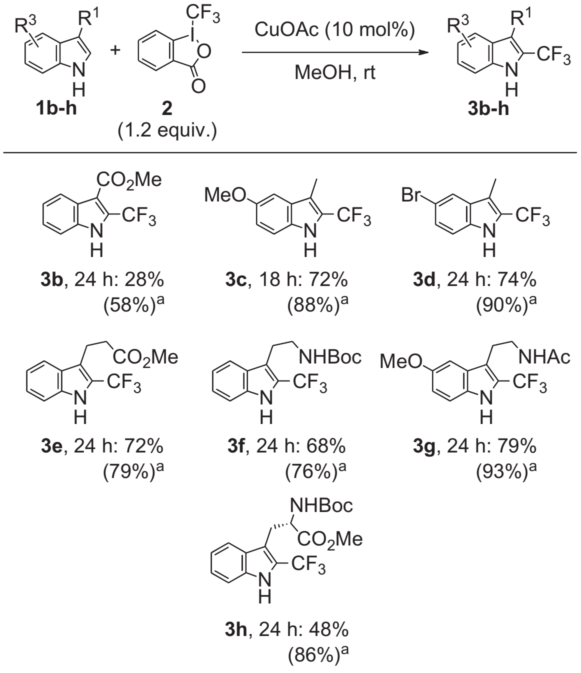
Table 1
Screening of reaction conditions[a]



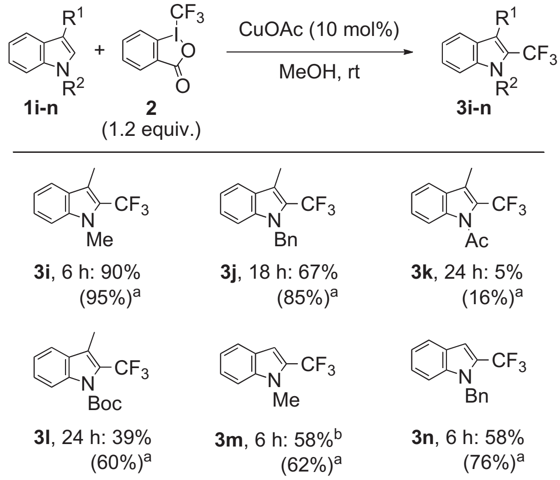
Entry	Catalyst	Solvent	Yield[b] (%)
1	None[c]	MeOH	N.R.[d]
2	$Fe(OAc)_2$	MeOH	58
3	$Co(OAc)_2$	MeOH	13
4	$Ni(OAc)_2$	MeOH	15
5	$Cu(OAc)_2$	MeOH	55
6	$Zn(OAc)_2$	MeOH	23
7	CuOAc	MeOH	79 (95)[e]
8	CuOAc	EtOH	55
9	CuOAc	MeCN	24
10	CuOAc	THF	51
11	CuOAc	CH_2Cl_2	68
12	CuOAc	Toluene	16

[a] The reactions were carried out in MeOH (1.5 ml) on a 0.15 mmol scale with catalyst (10 mol %) and **2** (1.2 equiv.) under an Ar atmosphere.
[b] Isolated yield.
[c] No catalyst was used.
[d] No reaction was observed.
[e] The number in parenthesis is yield based on recovered starting material.

results and an acceptable yield of **3a** was obtained by using CuOAc (entries 2, 5, and 7). In order to optimize the reaction conditions, the reaction solvent was next screened, as shown in Table 1 and MeOH was found to be the best solvent for the present reaction (entries 7–12). Although, *C*4-trifluoromethylated 3-methylindole was generated in less than 6% yield as a by-product in all cases, high *C*2-selectivity was observed.[16]



Scheme 2. Trifluoromethylation of 3-substituted indole derivatives. [a]The numbers in parentheses are yields based on recovered starting material.



Scheme 3. *C*2-selective trifluoromethylation of indole derivatives. [a]The numbers in parentheses are yields based on recovered starting material. [b]The reaction was carried out at 50 °C.[20]

Under the optimized conditions, we examined the trifluoromethylation of various *C*3-substituted indole derivatives (Scheme 2).[17] Introduction of an electron-withdrawing group at the *C*3 position diminished the reaction rate and yield (**3b**). Coupled with the result in the case of **1a**, this result suggests that the electronic properties of the five-membered ring of indoles are important for the present trifluoromethylation reaction. In contrast, substituents at *C*5 had less effect on the reaction (**3c** and **3d**). Since our reaction can be conducted under mild conditions, various functional groups were tolerant. Reactions of 3-(3-indolyl)propionic acid ester **1e**, tryptamine derivative **1f,** and melatonin **1g** proceeded without difficulty to give the *C*2-trifluoromethylated products **3e–g** in good yield. It is noteworthy that tryptophan derivative **1h** could be converted to the corresponding trifluoromethylated product **3h** without racemization under these reaction conditions.

Finally, the effect of a substituent at *N*1 position was investigated (Scheme 3). As expected, the reaction of *N*-alkylated 3-methylindoles proceeded smoothly with good to high yield. In particular, trifluoromethylated compound **3i** provided as high as 90% yield in the reaction of *N*-methyl 3-methylindole **1i**. In accord with the result in the case of **1b**, however, the reaction of **1k** and **1l** having electron-withdrawing group at *N*1 position resulted in low yield. When simple indole was subjected to our reaction, chemical yield was only 35%. To our delight, however, the yields of the desired products were enhanced by the introduction of a substituent at the *N*1 position. Notably, *C*2-trifluoromethylated products were obtained selectively in these reactions, even though, the *C*3 positions of **1m** and **1n** were not substituted in these cases (**3m**[18] and **3n**).[19]

In summary, we have demonstrated regioselective trifluoromethylation of indole derivatives catalyzed by CuOAc. This reaction proceeded under mild conditions with only a small excess of Togni's reagent and 10 mol % of the catalyst and selectively provided *C*2-trifluoromethylated indoles. Further study on the mechanism of this reaction is in progress.

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15. The reaction without methal catalyst in non-degassed solvent or under aerobic conditions gave a small amount of **3a**. This result is consistent with a previous report: see Ref. 8.
16. For example, the 4-trifluoromethylated derivative was obtained in 4% yield from the reaction described in entry 7 of Table 1.
17. *Typical procedure of trifluoromethylation of indoles*: To a solution of CuOAc (1.8 mg, 0.015 mmol) and hypervalent iodine reagent **2** (56.9 mg, 0.18 mmol) in degassed MeOH (1.5 ml) was added *N*-methyl-3-methylindole **1i** (21.8 mg, 0.15 mmol) under an argon atmosphere at room temperature. The reaction mixture was stirred for 6 h, then diluted with Et$_2$O. To the mixture was added saturated NaHCO$_3$ solution (0.5 ml), and the whole was extracted with Et$_2$O (3 ml × 3). The combined organic layer was dried over Na$_2$SO$_4$. The solid was filtered off and the filtrate was evaporated in vacuo. The residue was subjected to preparative TLC on silica gel to give trifluoromethylated compound **3i** as a yellowish oil (28.8 mg, 90%).
18. Although the inseparable mixture of regioisomers was obtained, careful analysis of the by-products revealed that 3- and 4-trifluoromethylated *N*-methylindoles were also formed in 13% and 7% yield, respectively.
19. Copper-catalyzed regioselective arylation of indoles with hypervalent iodine reagent has been reported, see: Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.
20. *N*-Methyl-2-trifluoromethylindole **3l** was obtained in 48% at room temperature.